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Synthesis of Condensed Tannins. Part 4.† A Direct Biomimetic Approach to [4,6]- and [4,8]-Biflavanoids

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The generation of flavanyl-4-carbo-cations from flavan-3,4-diols and their condensation with nucleophilic flavan-3-ols to form [4,6]- and [4,8]-biflavanoids at ambient temperatures and under mildly acidic aqueous conditions apparently simulates the initial step in condensed tannin formation in a number of natural sources. The stereospecificity (or stereoselectivity) of the reaction is conditioned mainly by the 2,3-*cis* or 2,3-*trans* stereochemistry of the parent flavan-3,4-diol, but also by the nucleophilicity of the flavan-3-ol, and its regiospecific (or regioselective) course by steric factors arising from variation in substitution of the receptive A-ring of the flavan-3-ol.

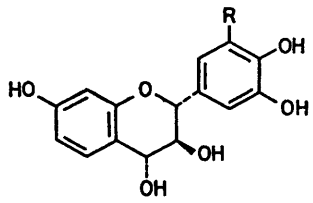
In recent communications [1-8] we have established a series of significant factors which should, with some refinement, assist in the unambiguous structural and stereochemical assignment of biflavonoids [6] and also of higher oligomeric condensed tannins.[7] These include definition of the optimum conditions for interflavanoid coupling; [2,3] prediction of its stereochemical course from electrophilic substitutions of flavanyl-4-carbocations on reactive phenolic nuclei; [2,3] application of circular dichroism and the phenolic quadrant rule to the stereochemistry at C-4 of the resultant 4-arylflavan-3-ol model compounds; [2-4] definition of the point of electrophilic substitution on (+)-catechin derivatives; [1,8] and also indications of the sensitive contribution by steric factors in governing the point of substitution.[2,5]

† Part 3 is the preceding paper.

These developments provide a new stimulus to the chemistry of condensed tannins and we now report more detailed results, of relevance to those biflavanoids which are distributed in over 1 000 species amongst the Leguminosae and Anacardiaceae.

RESULTS AND DISCUSSION

Our synthetic approach extends to a representative range of those [4,8]- and [4,6]-biflavanoids which are present, together with appropriate precursors, in the commercially important barks of *Acacia mearnsii* (black wattle) [9] and many related *Acacia* species,[10] and also in the heartwoods of *Schinopsis* spp. (quebracho), *Rhus lancea* (karee), and *Colophospermum mopane* (mopane); and to others which have as yet no natural counterparts. Thus, treatment of (2*R*,3*S*,4*R*)-flavan-3,3′,4,4′,7-pentaol



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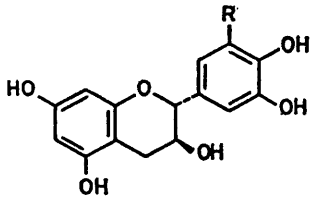
(2) R = OH



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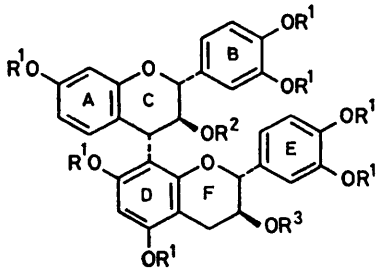
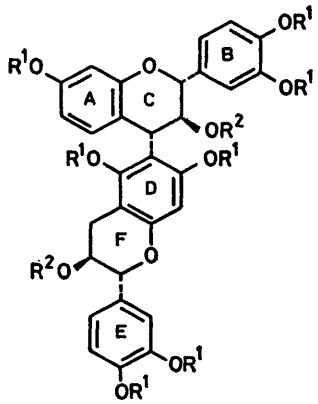


(5) $R^1=R^2=R^3=H$
(6) $R^1=R^2=Me$, $R^3=H$
(7) $R^1=R^2=Me$, $R^3=Ac$
(8) $R^1=Me$, $R^2=R^3=H$
(9) $R^1=Me$, $R^2=R^3=Ac$



(10) $R^1=R^2=H$
(11) $R^1=Me$, $R^2=H$
(12) $R^1=Me$, $R^2=Ac$

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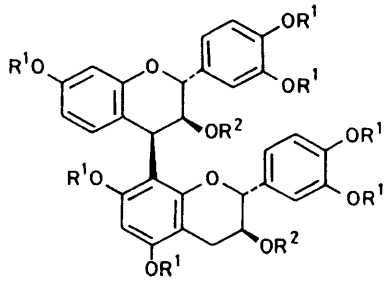
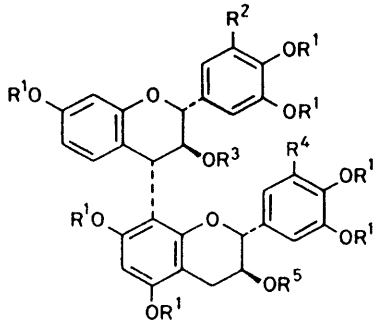
[(1), (+)-mollisacacidin] and (2*R*,3*S*)-flavan-3,3',4',5,7-pentaol [(3), (+)-catechin] with aqueous 0.1M HCl at ambient temperatures for 2 h gave a mixture of three biflavanoids (5), (10), and (13) [each comprised two flavan-3-ol units, (−)-fisetinidol (upper unit) and (+)-catechin (lower unit)] in 28, 5.5, and 16.5% yields respectively. Amongst these the predominant [4,8]-all-*trans* isomer (5) could be separated by preparative thin layer chromatography (p.l.c.), while the remaining [4,6]-all-*trans* (10) and [4,8]-2,3-*trans*-3,4-*cis*:2',3'-*trans* (13) isomers migrate as a mixture separable only by paper chromatography (p.c.). Similar condensation of (2*R*,3*S*,4*R*)-flavan-3,3',4,4',5',7-hexaol [(2), (+)-leucorobinetinidin] and (+)-catechin (3) also gives a mixture of the [4,8]- and [4,6]-all-*trans*-(−)-robinetinidol-(+)-catechin biflavanoid isomers [(16) and (20) respectively] and the [4,8]-3,4-*cis* isomer (23) in 23.0, 3.3, and 11.2% yields, respectively, and are separable as before by t.l.c. and p.c. Both the above reactions also proceed, albeit more slowly, in the presence of organic acids.



(13) $R^1=R^2=H$
(14) $R^1=Me$, $R^2=H$
(15) $R^1=Me$, $R^2=Ac$



(16) $R^1=R^3=R^4=R^5=H$, $R^2=OH$
(17) $R^1=Me$, $R^2=OMe$, $R^3=R^4=R^5=H$
(18) $R^1=Me$, $R^2=OMe$, $R^3=R^5=Ac$, $R^4=H$
(19) $R^1=R^3=R^5=H$, $R^2=R^4=OH$

The products of the reactions are identified by methylation with diazomethane and the methyl ethers acetylated to give their diacetates. Their n.m.r. spectra show temperature-dependent line-widths due mainly to rotational (and possibly contributory conformational) isomerism about the inter-flavanoid bonds;[11] the degree of line-broadening and/or duplication of broadened resonances being simply overcome by sharpening or coalescence at elevated temperatures, thus enabling spectral interpretations. The diacetates of the [4,8]-diastereoisomers [(9), (15)] are readily distinguishable from the diacetate of the [4,6]-isomer by the absolute chemical shifts of the residual D-ring protons in the aromatic region (δ 6.15, 6.13, and 6.26 respectively) and the relative chemical shifts of the first-mentioned pair [Δδ (6-H, 8-H) 0.11].[1] Their relative stereochemistry is deduced by comparing their coupling constants with those of synthetic 4-arylflavan-3-ol analogues.[3] For all 2,3-*trans*-biflavanoids, their 3,4-*trans* or 3,4-*cis* stereochemistry is also readily differentiated by the characteristic splitting patterns and pronounced downfield positions of H-3 triplets (δ 5.9—6.1, ΣJ_s *ca.* 20 Hz) of the former relative to the corresponding quartets (δ 5.3—5.6, ΣJ_s *ca.* 15.5 Hz) of the latter. The absolute configurations at C-4 are accordingly self-evident, and are supported by negative Cotton effects in the c.d. spectra of (5), (10), (16), and (20), and positive Cotton effects for (13) and (23).[6] The all-*trans*-biflavanoids [*e.g.* (5), (37), (48), (51), and (56)] are also characterized by the formation of 3-*O*-methyl ethers of the upper unit [*e.g.* (6), (38), (49), (52), and (57)] during methylations with diazomethane.

The above condensations led to a re-examination of the natural biflavanoids A, B, and D [corresponding to (5), (16), and (19)[9]], representing some of the major components of the commercially-important black wattle bark ('Mimosa') extract. Fraction A of the extract yields two (−)-fisetinidol-(+)-catechin biflavanoids (5) and (13), with heptamethyl ether diacetates [(9) and (15) respectively] identical to those of their synthetic [4,8]-all-*trans* and [4,8]-3,4-*cis* counterparts by ^1H n.m.r. spectroscopy, m.s., and c.d., differences in the high-intensity Cotton effects at *ca.* 220 nm (negative and positive, respectively) being highly diagnostic. The natural [4,8]-2,3-*trans*-3,4-*cis*:2,3-*trans*-(−)-fisetinidol-(+)-catechin (13), previously overlooked, represents the major component in fraction A of the bark extract of *A. mearnsii*, whereas the minor component, the all-*trans*-diastereoisomer (5), predominates amongst the products of synthesis. The [4,6]-all-*trans* structural isomer was not observed in fraction A of the extract. The [4,8]-(−)-robinetinidol-(+)-catechin [(16), component B, identical to the synthetic product] and [4,8]-(−)-robinetinidol-(+)-gallocatechin [(19), component D] (H-6 singlets of their methyl ether diacetates at δ 6.13 and 6.17 respectively) are not accompanied by 3,4-*cis*-diastereoisomers; but both possess the same 2*R*,3*S*,4*S*:2*R*,3*S* absolute configuration as the analogue (5), as may be inferred from c.d. comparison of the same derivatives.[6] Significantly the group of four biflavanoids (5), (13), (16), and (19), are accompanied in black wattle bark by those flavanoids [(+)-mollisacacidin (1), (+)-leucorobinetinidin (2), (+)-catechin (3), and (+)-gallocatechin (4)][12] which may be employed in their *in*

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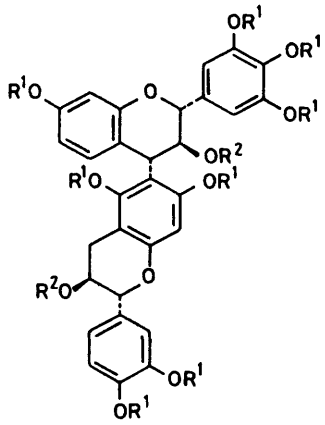
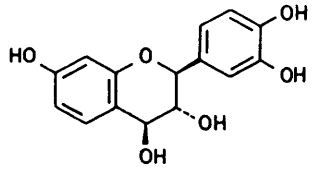
vitro synthesis, and they in turn may serve as precursors for a group of five ' branch-chain ' triflavanoids [7] present in the same source.

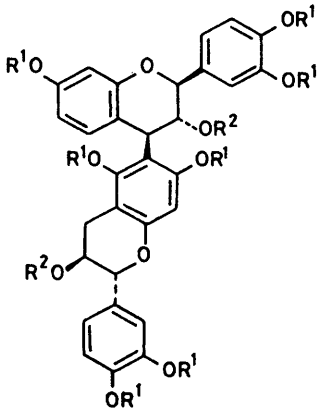
Under identical conditions 2*S*,3*R*,4*S*-flavan-3,3',4,4',-7-pentaol [(26), (−)-leucofisetinidin], the enantiomer of (+)-mollisacacidin (1), combined with (+)-catechin (3) shifts of their 6- and 8-protons (δ 6.05, 6.24, and 6.08 respectively), and also from the diastereoisomers cited above by their reversed low-wavelength, high-intensity Cotton effects in the c.d. spectra [(27) and (30) positive, (33) negative]. Accordingly their absolute configurations are assigned as 2*S*,3*R*,4*R*:2*R*,3*S* for the [4,8]- and



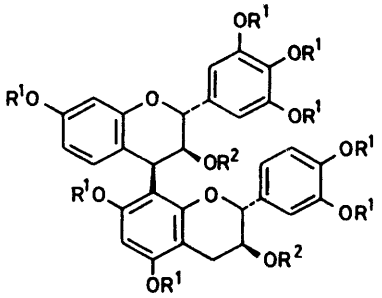
(20) $R^1=R^2=H$
(21) $R^1=Me$, $R^2=H$
(22) $R^1=Me$, $R^2=Ac$



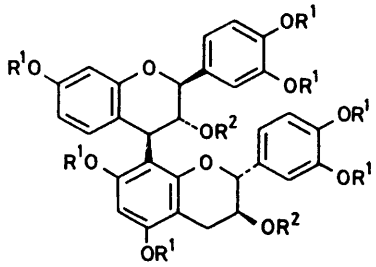
(26)



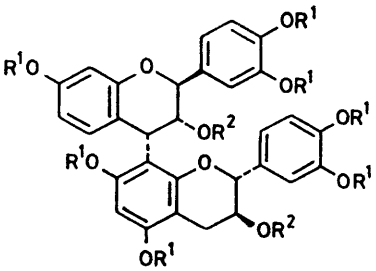
(30) $R^1=R^2=H$
(31) $R^1=Me$, $R^2=H$
(32) $R^1=Me$, $R^2=Ac$



(23) $R^1=R^2=H$
(24) $R^1=Me$, $R^2=H$
(25) $R^1=Me$, $R^2=Ac$



(27) $R^1=R^2=H$
(28) $R^1=Me$, $R^2=H$
(29) $R^1=Me$, $R^2=Ac$



(33) $R^1=R^2=H$
(34) $R^1=Me$, $R^2=H$
(35) $R^1=Me$, $R^2=Ac$

giving three biflavanoids (27), (30), and (33) in 24.8, 1.9, and 19.6% yields respectively. These products accordingly represent diastereoisomers of (5), (10), and (13), the ' upper ' units of the two groups bearing an enantiomeric relationship, but with the ' lower ' (+)-catechin unit as common denominator. These products were distinguished from each other as before by a combination of coupling constants ($J_{3,4}$) and the chemical

[4,6]-all-*trans* isomers [(27), (30)] and 2*S*,3*R*,4*S*:2*R*,3*S* for the [4,8]-3,4-*cis* isomer (33). As in the parallel case of wattle bark extract, the pair of [4,8]-(−)-leucofisetinidin-(+)-catechin diastereoisomers [(27), (33)] were both readily isolated from those heartwoods, *i.e. Rhus lancea*,[13] *Schinopsis balansae*, and *S. lorentzii* [14] in which (−)-leucofisetinidin [(2*S*,3*R*,4*S*)-(26)] and (+)-catechin [(2*R*,3*S*)-(3)] represent the predominant flavonoid species

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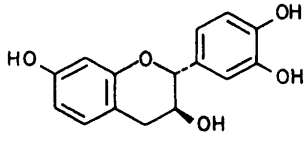
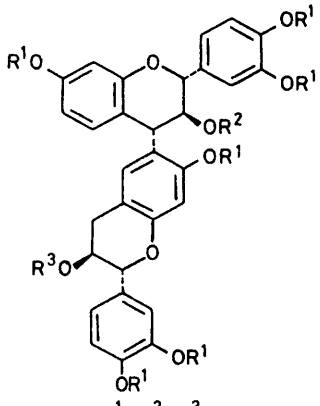
at the heartwood–sapwood interface, declining in concentration with increasing age of the heartwood with progressive tannin formation.[13]

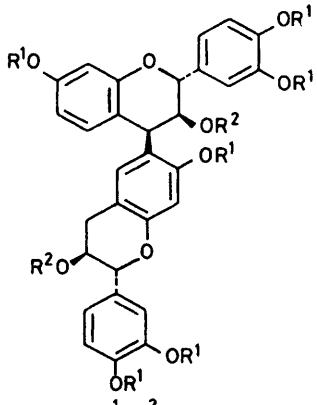
While the course of the above *in vitro* condensations, for the molar ratios (1 : 4—8) employed, is both regio-



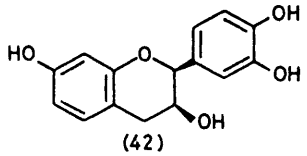
(36)



(37) $R^1=R^2=R^3=H$
(38) $R^1=R^2=Me$, $R^3=Ac$
(39) $R^1=Me$, $R^2=R^3=Ac$



(40) $R^1=R^2=H$
(41) $R^1=Me$, $R^2=Ac$



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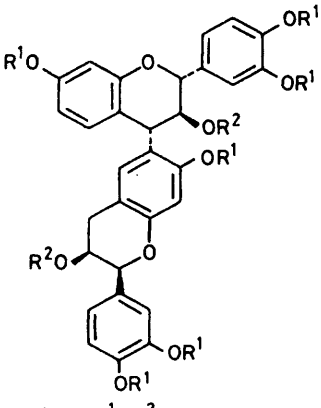
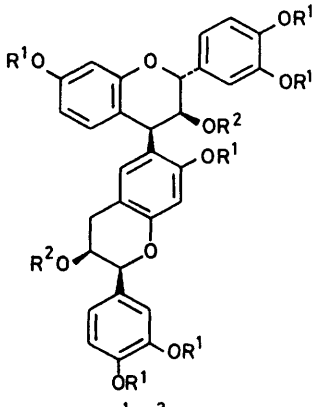


(43) $R^1=R^2=H$
(44) $R^1=Me$, $R^2=Ac$



(45) $R^1=R^2=H$
(46) $R^1=Me$, $R^2=Ac$

selective (8- : 6-substitution ratio 7—54 : 1) * and stereoselective (3,4-*trans* : 3,4-*cis* ratio 1.25—1.7 : 1), we now elected to extend the coupling reaction to resorcinol-type flavan-3-ols in order to examine the dual effects of reduced steric hindrance and reduced nucleophilicity of the resorcinol A-ring; the existence of resorcinol–resorcinol-type biflavanoids is known from our previous work.[15] Thus (+)-mollisacacidin [(2*R*,3*S*,4*R*)-(1)] and (—)-fisetinidol [(2*R*,3*S*)-(36)] condense regiospecifically at C-6 on the flavan-3-ol unit, as well as stereoselectively, under the same conditions as above forming the [4,6]-all-*trans* (37) and [4,6]-3,4-*cis*-bis-(—)-fisetinidols (40) in similar total overall yields (27.0 and 19.0%, respectively) as in the above couplings with (+)-catechin. N.m.r. spectra of the hexamethyl ether diacetates of all [4,6]-biflavanoids of the resorcinol–resorcinol type are characterized by the complete absence of line-broadening or duplication phenomena associated with rotational isomerism, in contrast to those of the corresponding derivatives of [4,6]- and [4,8]-biflavanoids of the resorcinol–phloroglucinol type (see above). The 4,6-linkages are established by observation of two singlets in the high-field aromatic region of the 360-MHz n.m.r. spectra of the diacetates of each compound (*cf.* Figure 1) and the 3,4-stereochemistry by the appropriate coupling constants ($J_{3,4}$ 9.0 and 5.0 Hz, respectively) and high intensity negative and positive Cotton effects at 220 nm. These novel [4,6]-bis-(—)-fisetinidols of 2*R*,3*S*,4*R*:2*R*,3*S* (37) and 2*R*,3*S*,4*S*:2*R*,3*S* (40) absolute configurations find their natural counterparts in the heartwood of the mopane tree (*Colophospermum mopane*) in co-existence with both (+)-2,3-*trans*-3,4-*cis*-leucofisetinidin and (—)-fisetinidol (36) [15] as their potential precursors. They represent the first natural biflavanoids in which the A-rings of both flavanoid moieties are resorcinol units.

Confirmation of the regiospecificity of the above condensation and simultaneous examination of the possible effect of the 2,3-*cis* stereochemistry of the nucleophile was attempted by reaction of (+)-mollisacacidin (1) with (+)-epifisetinidol [(2*S*,3*S*)-(42)] the latter a component of unusual stereochemistry in *C. mopane*.[16] As before the reaction proceeds regiospecifically at C-6 (high-field singlets in the aromatic region at 360 MHz, *cf.* Figure 1) giving [4,6]-2,3-*trans*-3,4-*trans*:2′,3′-*cis*-(43) and [4,6]-2,3-*trans*-3,4-*cis*:2′,3′-*cis*- (45) -(—)-fisetinidol-(+)-epifisetinidol biflavanoids of 2*R*,3*S*,4*R*:2*S*,3*S* and 2*R*,3*S*,4*S*:2*S*,3*S* configuration, respectively (21.0 and 16% yields). These 2,3-*cis*-biflavanoids have, as yet, no counterpart in nature. The above reactions with fisetinidols as nucleophiles proceed at the same speed and produce similar yields of products, compared with the more strongly nucleophilic but sterically more hindered condensations with (+)-catechin.

(—)-Epicatechin [(2*R*,3*R*)-(47), enantiomeric to (+)-epifisetinidol], long since known as a ' terminal ' group in biflavanoids,[17-19] follows the now expected course of regioselective and stereoselective condensation with (+)-mollisacacidin (1) to form the predominantly [4,8]-all-*trans*-isomer [(2*R*,3*S*,4*S*:2*R*,3*R*)-(48)], its [4,8]-3,4-*cis* analogue [(2*R*,3*S*,4*R*:2*R*,3*R*)-(53)] and also [4,6]-all-*trans*-(+)-fisetinidol-(—)-epicatechin [(2*R*,3*S*,4*S*:2*R*,-3*R*)-(51)] in minor proportion (30.0, 24.0, and 1.0%

* As in the bromination of (+)-catechin (2.5 : 1), where an equimolar ratio of reagents is used.

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yields respectively). Natural counterparts of these compounds are also unknown.

In these series of condensations yet another variable was introduced by reacting, as 2,3-*cis*-flavan-3,4-diol, (−)-teracacidin [(2*R*,3*R*,4*R*)-(55)], with (+)-catechin (3). As observed in its condensation with phloroglucinol,[2,3] the course of the reaction was stereospecific represented by phloroglucinol-type flavan-3-ols, the reduction product ($NaBH_4$) of (+)-dihydroquercetin, *i.e.* the (+)-procyanidin [(2*R*,3*S*,4*R* or *S*)-(61)] and (+)-catechin (3) condensed as before, but without isolation of the highly unstable flavan-3,4-diol, gives [4,8]- and [4,6]-all-*trans*-bis-(+)-catechins [(62), (64)] in 15.1 and 4.8% yields, respectively, based on (+)-taxifolin as

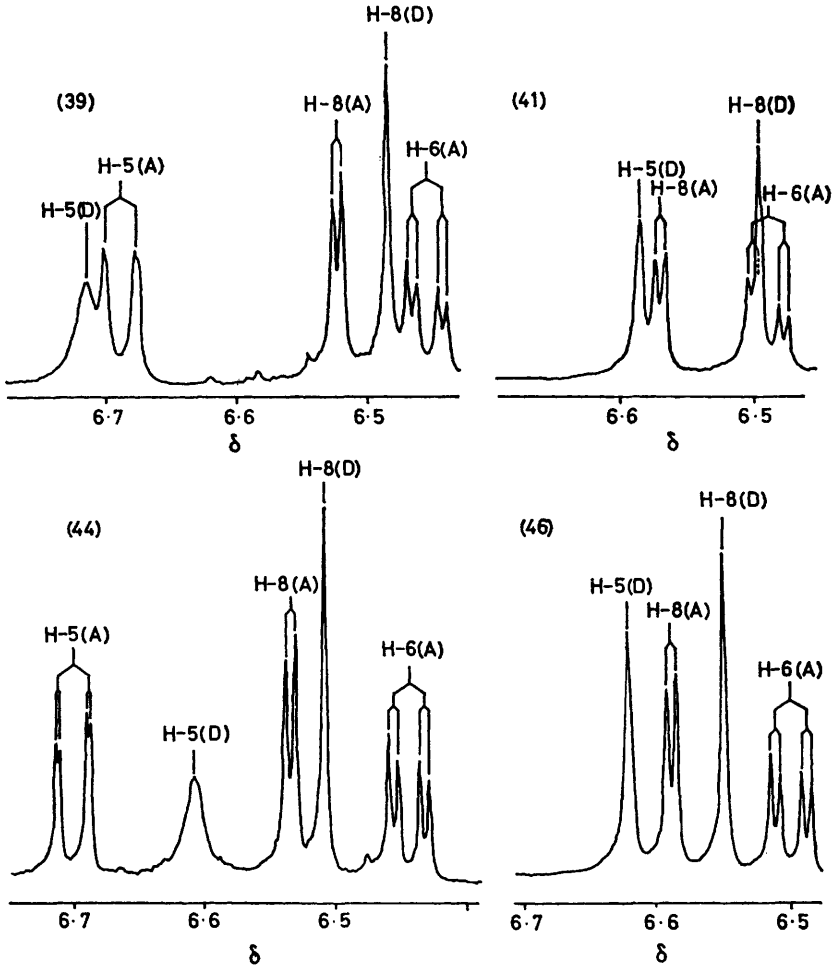

FIGURE Expanded high-field aromatic resonances from ^1H n.m.r. 360-MHz spectra of the hexamethyl ether di-*O*-acetyl derivatives of 2,3-*trans*-3,4-*trans*:2′,3′-*trans*- (39); 2,3-*trans*-3,4-*cis*:2′,3′-*trans*- (41); 2,3-*trans*-3,4-*trans*:2′,3′-*cis*- (44); and 2,3-*trans*-3,4-*cis*:2′,3′-*cis*- (46) bifisetinidols

but in this instance also regioselective yielding two products only, [4,8]- and [4,6]-2,3-*cis*-3,4-*trans*:2,3-*trans*-isomers [(56), (59)], both having 2*R*,3*R*,4*R*:2*R*,3*S* configurations. Attack by (+)-catechin on the flavanyl 4-carbo-cation is presumably from the less hindered 'upper' side,[2,3] doubtlessly involving neighbouring-group participation by the 3-*axial* hydroxy-group. The yields of products, 41.0 and 9.0% [(56), (59), respectively], again reflect the lower steric hindrance at C-8 relative to C-6 on (+)-catechin.

Finally, in order to assess the versatility of the method as regards synthesis of biflavanoids and eventually higher oligomeric procyanidins in which all units are starting material. The conspicuous absence of the [4,8]-3,4-*cis*-isomer indicates that the reaction follows a stereospecific course, while the relatively low yields may also be indicative of a high degree of self-condensation of the (+)-procyanidin under the conditions employed. This condensation contrasts with the indirect method developed by Haslam *et al.*[20] in which toluene-α-thiol is reacted with procyanidin tannins of unknown absolute configuration in order to obtain 2,3-*trans*-3,4-*cis*-4-toluenethiol ether derivatives which are in turn subjected to condensation with (+)-catechin.

The above series of direct condensations illustrate the versatility of a simple and relatively high yield (37—

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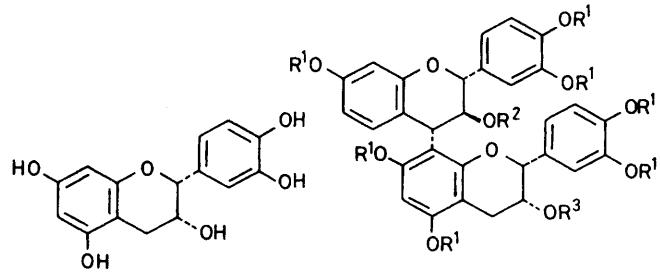
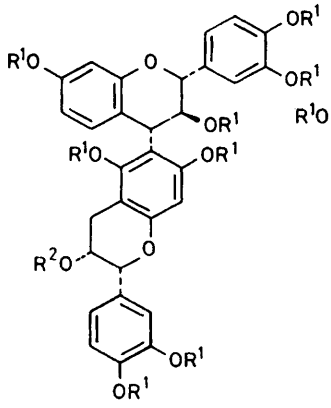
55%) general method in which the reaction course is determined by the structure and stereochemistry of the participating species, including the role of steric factors conditioned by the bulk of the flavanyl-4-cation and of the nucleophilic flavan-3-ols; the nucleophilicity and functionalization of the A-ring of the latter; and the 2,3-stereochemistry of the parent flavan-3,4-diol. The mild conditions applied avoid anthocyanidin formation; limit self-condensation of both reactants, particularly the flavan-3,4-diol; and avoid ring opening or inversion at C-2. The aqueous conditions simulate natural condensations, enabling syntheses of free-phenolic biflavanoids of known absolute configuration and permitting extension to triflavanoids[7] which exhibit mild affinity for collagen substrates. The natural

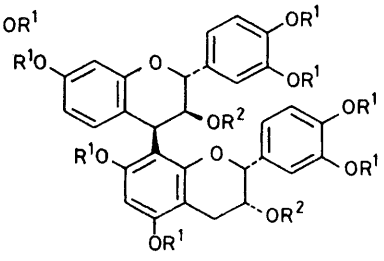


(47)

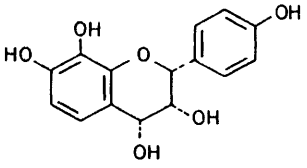
(48) $R^1=R^2=R^3=H$
(49) $R^1=R^2=Me$, $R^3=Ac$
(50) $R^1=Me$, $R^2=R^3=Ac$



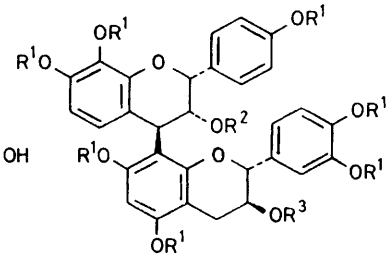
(51) $R^1=R^2=H$
(52) $R^1=Me$, $R^2=Ac$



(53) $R^1=R^2=H$
(54) $R^1=Me$, $R^2=Ac$

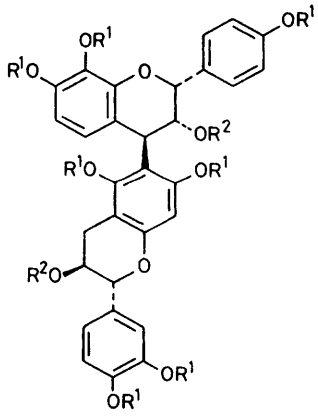


(55)

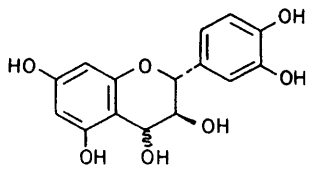


(56) $R^1=R^2=R^3=H$
(57) $R^1=R^2=Me$, $R^3=Ac$
(58) $R^1=Me$, $R^2=R^3=Ac$

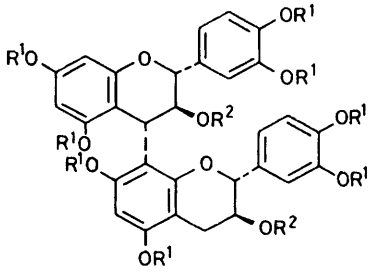
association of biflavanoids and constituent flavan-3,4-diols, and nucleophilic flavan-3-ols of the same structure and 2,3-absolute configuration in a number of natural sources, and the analogies evident from *in vitro* syntheses of biflavanoids are indicative of a flavanyl-4-carbocation mediated condensation rather than the earlier quinone methide and flav-3-en-3-ol mechanisms proposed by Haslam *et al.*[18,21]



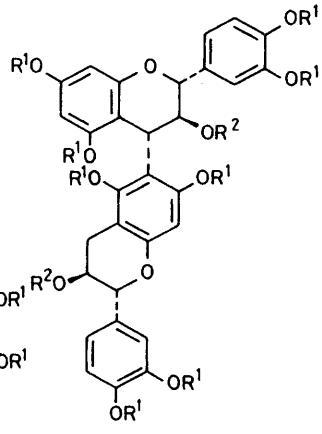
(59) $R^1=R^2=H$
(60) $R^1=Me$, $R^2=Ac$



(61)



(62) $R^1=R^2=H$
(63) $R^1=Me$, $R^2=Ac$



(64) $R^1=R^2=H$
(65) $R^1=Me$, $R^2=Ac$

EXPERIMENTAL

T.l.c. was performed on DC-Plastikfolin Kieselgel 60 F_{254} (0.25 mm) and the plates sprayed with H_2SO_4–HCHO (40 : 1) after development. Preparative plates [Kieselgel PF_{254} (1.0 mm)] were air-dried and used without prior activation. Methylations were performed with an excess of diazomethane in methanol–diethyl ether at −15 °C for 48 h, while acetylations were carried out with acetic anhydride–pyridine. Evaporations were performed under reduced pressure at *ca.* 50 °C. ^1H N.m.r. spectra were recorded on Bruker WP-80 and WH-360 FT spectrometers for solutions in $CDCl_3$ at 37 °C (unless stated otherwise) with $SiMe_4$ as internal standard, mass spectral data on a Varian CH-5 instrument, and circular dichroism data on a JASCO J-20 spectropolarimeter. Analyses (C and H) were performed by Analytische Laboratorien, Fritz-Pregl-Strasse 24, 5270 Gummersbach 1 Elbach, Germany.

General Condensation and Work-up Procedures.—The flavan-3,4-diol (*ca.* 0.002 mol) and flavan-3-ol unit (*ca.* 0.016 mol) were dissolved in 0.1M HCl (250 ml) and the mixture stirred at room temperature (*ca.* 23 °C). After addition of water (250 ml), the mixture was extracted with ethyl acetate (4 × 150 ml) and the combined extracts dried (Na_2SO_4). Evaporation of the solvent followed by p.l.c. separation [benzene–acetone–methanol (6 : 3 : 1)] afforded the free phenolic biflavonoids.

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(+)-*Mollisacacidin*–(+)-*Catechin Condensation*.—Coupling of (+)-mollisacacidin (1), (580 mg) with (+)-catechin (3) (4.64 g) for 2 h affords two bands, R_F 0.42 (249 mg, 22%) and 0.33 (322 mg, 28%): (*a*) The R_F 0.42 fraction consists of a mixture of (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*cis*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (13) and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-6-yl]flavan (10). Methylation of this free phenolic mixture (240 mg) followed by p.l.c. separation [benzene–acetone (8 : 2)] gave two bands, R_F 0.28 (104 mg) and 0.22 (35 mg); the former consisted of the 4,8-coupled 3,4-*cis*-heptamethyl ether (14) as a colourless solid, and the latter of the 4,6-linked all-*trans*-heptamethyl ether (11), also as a colourless solid.

(2R,3S,4R)-2,3-trans-3,4-cis-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3′,4′,7-*trimethoxyflavan* (15).—Acetylation of the 4,8-linked 3,4-*cis*-heptamethyl ether (14) (60 mg) followed by p.l.c. separation [benzene–acetone (9 : 1)] afforded the *diacetate* (15), R_F 0.18, as a colourless solid (38 mg); *m/e* 774 (M^+, 81%), 684 (76), 624 (80), 522 (10.6), 491 (89), 462 (83), 449 (67), 431 (64), 387 (5.9), 357 (13.9), 327 (53), 300 (6.2), 297 (70), 269 (100), 222 (7.9), 180 (75), and 151 (90); δ 6.57—5.72 (m, 10 H, aromatic), 6.13 [s, 6-H(D)], 5.73 [d, 8-H(A), *J* 2.5 Hz], 5.54 [dd, 3-H(C), *J* 6.5 and 9.0 Hz], 5.26 d, 2-H(C), *J* 9.0 Hz], 4.90 [d, 4-H(C), *J* 6.5 Hz], 5.16—4.81 [m, 3-H(F)], 4.07 [d, 2-H(F), *J* 8.5 Hz], 3.81, 3.79, 3.73, 3.69 (4 × s, 6 × OMe), 3.46(s) and 3.32(s) [Δν 11.3 Hz, 7-OMe(D)], 3.12 [dd, 4-eq-H(F), *J* 6.3 and 16.9 Hz], 2.54 [dd, 4-ax-H(F), *J* 8.5 and 16.9 Hz], 1.94(s) and 1.80(s) [Δν 11.9 Hz, 3-OAc(F)], and 1.77(s) and 1.71(s) [Δν 4.4 Hz, 3-OAc(C)]; $\Delta G^{\ddagger}_{rot.}$ 18.04 kcal mol^{-1}; c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{280}$ +2 424, $[\theta]_{265}$ +303, $[\theta]_{232}$ +41 818, and $[\theta]_{209}$ 0 (Found: C, 66.0; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(2R,3S,4S)-2,3-trans-3,4-trans-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-6-*yl*]-3′,4′,7-*trimethoxyflavan* (12).—Acetylation of the 4,6-linked all-*trans*-heptamethyl ether (11) (26 mg) gave the *diacetate* (12) (24 mg) as a colourless solid; *m/e* 744 (M^+, 9.7%), 684 (100), 624 (24), 491 (59), 462 (55), 449 (57), 431 (63), 387 (6.1), 357 (5.3), 327 (15.3), 300 (4.7), 297 (64), 269 (70), 222 (16.8), 180 (67), and 151 (90); δ 7.12—6.26 (m, 10 H, aromatic), 6.26 [s, 8-H(D)], 6.08 [t, 3-H(C), ΣJ_s 20.0 Hz], 5.28 [m, 3-H(F)], 4.91 [d, 2-H(F), *J* 7.5 Hz], 4.89 [d, 4-H(C), *J* 10.0 Hz], 4.67 [d, 2-H(C), *J* 10.0 Hz], 3.88, 3.83, 3.75, 3.72, 3.53 (5 × s, 7 × OMe), 3.17 [dd, 4-eq-H(F), *J* 5.8 and 15.8 Hz], 2.76 [dd, 4-ax-H(F), *J* 7.5 and 15.8 Hz], 1.90(s) and 1.86(s) [Δν 3.8 Hz, 3-OAc(F)], and 1.61 [s, 3-OAc(C)]; $\Delta G^{\ddagger}_{rot.}$ 17.13 kcal mol^{-1}; c.d. (MeOH) $[\theta]_{295}$ 0, $[\theta]_{280}$ −4 393, $[\theta]_{268}$ 0, $[\theta]_{260}$ +606, $[\theta]_{245}$ 0, $[\theta]_{228}$ −41 818, and $[\theta]_{210}$ −2 121 (Found: C, 66.0; H, 6.1. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(*b*) The R_F 0.33 fraction consisted of the free phenolic (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]-flavan (5) [9] as a light brown solid. Methylation of the free phenol (310 mg) followed by p.l.c. separation [benzene–acetone ×2 (8 : 2)] afforded two fractions, R_F 0.43 (28 mg) and 0.21 (151 mg). The former band consisted of the 4,8-linked all-*trans*-octamethyl ether (6) and the latter of the 4,8-coupled all-*trans*-heptamethyl ether (8), both as white solids.

(2R,3S,4S)-2,3-trans-3,4-trans-4-[(2R,3S)-2,3-trans-3-*Acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3,3′,4′,7-*tetramethoxy flavan* (7).—Acetylation of the octamethyl ether (6) (22 mg) followed by p.l.c. separation [chloroform–acetone (19 : 1)] afforded the *monoacetate* (7), R_F 0.67 as a colourless solid (5 mg); *m/e* 716 (M^+, 59%), 684 (13.3), 624 (24), 494 (9.1), 491 (100), 462 (26), 461 (11.3), 449 (41), 387 (3.6), 329 (7.9), 327 (14.0), 300 (5.3), 297 (36), 269 (77), 222 (11.8), 194 (72), 180 (27), 179 (55), and 151 (60); δ 7.02—6.05 (m, 10 H, aromatic), 6.21 [s, 6-H(D)], 5.33—4.87 [m, 3-H(F)], 4.83 [d, 2-H(F) and 4-H(C), *J* 8.8 Hz], 4.69 [d, 2-H(C), *J* 9.4 Hz], 4.08 [dd, 3-H(C), *J* 8.8 and 9.4 Hz], 3.87, 3.83, 3.71, 3.70, 3.62 (5 × s, 7 × OMe), 2.99 [dd, 4-eq-H(F), *J* 5.6 and 15.8 Hz], 2.67 [d, 3-OMe(C)], 2.60 [dd, 4-ax-H(F), *J* 7.5 and 15.8 Hz], and 2.02(s), 1.86(s) [Δν 12.5 Hz, 3-OAc(F)].

(2R,3S,4S)-2,3-trans-3,4-trans-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3′,4′,7-*trimethoxyflavan* (9).—Acetylation of the heptamethyl ether (8) (100 mg) and subsequent p.l.c. separation [chloroform–hexane–acetone (90 : 6 : 4)] gave the diacetate (9) (R_F 0.44) as a colourless solid [9] (74 mg); *m/e* 744 (M^+, 4.8%), 684 (100), 624 (88), 491 (34), 462 (86), 449 (40), 431 (83), 387 (6.3), 357 (4.2), 327 (56), 300 (6.7), 297 (47), 269 (92), 222 (7.5), 180 (72), and 151 (97); δ 6.96—6.15 (m, 10 H, aromatic), 6.15 [s, 6-H(D)], 6.03 [t, 3-H(C), ΣJ_s 19.0 Hz], *ca.* 4.78 [m, 2-H(F) + 3-H(F)], 4.78 [d, 2-H(C), *J* 10.0 Hz], 4.77 [d, 4-H(C), *J* 9.0 Hz], 3.83, 3.80, 3.79, 3.69, 3.54 (5 × s, 7 × OMe), 3.09 [dd, 4-eq-H(F), *J* 6.3 and 16.9 Hz], 2.57 [dd, 4-ax-H(F), *J* 8.1 and 16.9 Hz], 2.04(s) and 1.84(s) [Δν 10.0 Hz, 3-OAc(F)], and 1.63(s), 1.56(s) [Δν 5.6 Hz, 3-OAc(C)]; $\Delta G^{\ddagger}_{rot.}$ 16.8 kcal mol^{-1}; c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{280}$ −2 424, $[\theta]_{274}$ 0, $[\theta]_{265}$ +4 242, $[\theta]_{248}$ 0, $[\theta]_{230}$ −45 454, $[\theta]_{210}$ −6 666 (Found: C, 66.0; H, 6.2. Calculated for $C_{41}H_{44}O_{13}$: C, 66.1; H, 6.0%).

(+)-*Leucorobinetinidin*–(+)-*Catechin Condensation*.—Reaction of (+)-leucorobinetinidin (2) (500 mg) with (+)-catechin (3) (3.79 g) for 2 h afforded two fractions, R_F 0.42 (137 mg, 14.5%) and 0.21 (217 mg, 23%). (*a*) The R_F 0.42 band consisted of a mixture of (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*cis*-3,3′,4′,5′,7-pentahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (23) and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,5′,7-pentahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-6-yl]-flavan (20). Methylation of this free phenolic mixture (130 mg) and subsequent p.l.c. separation [benzene–acetone (8 : 2)] gave two bands, R_F 0.34 (70 mg) and 0.28 (21 mg). The former fraction consisted of the 4,8-coupled 3,4-*cis*-octamethyl ether (24) and the latter of the 4,6-linked all-*trans*-octamethyl ether (21), both as colourless solids.

(2R,3S,4R)-2,3-trans-3,4-cis-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3′,4′,5′,7-*tetramethoxyflavan* (25).—Acetylation of the 4,8-linked 3,4-*cis*-octamethyl ether (24) (65 mg) followed by p.l.c. separation [benzene–acetone (9 : 1)] afforded the *diacetate* (25), R_F 0.24, as a colourless solid (45 mg); *m/e* 774 (M^+, 33%), 714 (56), 654 (40), 552 (2.0), 491 (67), 492 (66), 449 (11.6), 431 (4.5), 387 (2.0), 327 (37), 300 (2.4), 269 (100), 252 (9.1), 210 (18.5), 181 (40), and 151 (41); δ 6.79—5.79 (m, 9 H, aromatic), 6.13 [s, 6-H(D)], 5.54 [dd, 3-H(C), *J* 6.5 and 9.0 Hz], 5.24 [d, 2-H(C), *J* 9.0 Hz], 5.16—4.97 [m, 3-H(F)], 4.90 [d, 4-H(C), *J* 6.5 Hz], 4.13 [d, 2-H(F), *J* 8.5 Hz], 3.82, 3.81, 3.79, 3.71, 3.49, 3.31 (6 × s, 8 × OMe), 3.10 [dd, 4-eq-H(F), *J* 6.3 and 16.5 Hz], 2.56 [dd, 4-ax-H(F), *J* 8.0 and 16.5 Hz], 1.97(s) and 1.80(s) [Δν 13.8 Hz, 3-OAc(F)], and 8.22(s), 8.26(s) [Δν 3.8 Hz, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{295}$ 0, $[\theta]_{283}$ +2 727, $[\theta]_{277}$ 0, $[\theta]_{270}$ −3 939, $[\theta]_{257}$ 0, $[\theta]_{237}$ +53 030,

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and $[\theta]_{209}$ 0 (Found: C, 65.0; H, 6.3. $C_{42}H_{46}O_{14}$ requires C, 65.1; H, 6.0%).

(2R, 3S,4S)-2,3-trans-3,4-trans-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-6-*yl*]-3′,4′,5′,7-*tetramethoxyflavan* (22).—Acetylation of the 4,6-linked all-*trans*-octamethyl ether (21) (19 mg) and subsequent p.l.c. separation [benzene–acetone (9 : 1)] gave the *diacetate* (22) (R_F 0.28) as a colourless solid (12 mg); *m/e* 774 (M^+, 3.0%), 714 (100), 654 (9.9), 492 (9.9), 491 (12.3), 449 (11.5), 431 (4.0), 387 (1.7), 327 (58), 300 (1.1), 269 (35), 252 (2.4), 210 (16.4), 181 (35), 180 (23), and 151 (35); δ 7.0—6.25 (m, 9 H, aromatic), 6.26 [s, 8-H(D)], 6.11 [t, 3-H(C), ΣJ_s 20.0 Hz], 5.30 [m, 3-H(F)], 4.95 [d, 2-H(F), *J* 7.5 Hz], 4.89 [d, 4-H(C), *J* 10.0 Hz], 4.69 [d, 2-H(C), *J* 10.0 Hz], 3.86, 3.81, 3.73, 3.72, 3.52 (5 × s, 8 × OMe), 3.16 [dd, 4-eq-H(F), *J* 5.5 and 16.0 Hz], 2.77 [dd, 4-eq-H(F), *J* 8.0 and 16.0 Hz], 1.91(s), 1.86(s) [Δν 3.8 Hz, 3-OAc(F)], and 1.65(s), 1.56(s) [Δν 6.9 Hz, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{308}$ 0, $[\theta]_{251}$ −6 666, $[\theta]_{258}$ 0, $[\theta]_{237}$ −20 000, $[\theta]_{232}$ −10 303, $[\theta]_{229}$ −16 363, and $[\theta]_{218}$ 0 (Found: C, 65.1; H, 6.2. $C_{42}H_{46}O_{14}$ requires C, 65.1; H, 6.0%).

(*b*) The R_F 0.21 fraction gave the free phenolic (2*R*,3*S*,-4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,5′,7-pentahydroxy-4-[(2*R*,-3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (16) [9] as a light brown solid. Methylation of the free phenol (310 mg) and p.l.c. separation [benzene–acetone (8 : 2)] gave the all-*trans*-octamethyl ether (17), R_F 0.26, as a colourless solid (157 mg) which was acetylated (80 mg) and the resultant mixture resolved by p.l.c. [benzene–acetone (9 : 1)]. The *diacetate* (18), R_F 0.24, was obtained as a colourless solid (44 mg); *m/e* 774 (M^+, 1.2%), 714 (100), 654 (47), 492 (48), 491 (28), 449 (5.6), 431 (3.3), 387 (1.8), 327 (38), 300 (1.7), 269 (61), 252 (3.3), 210 (16.6), 181 (52), 180 (20), and 151 (45); δ 6.97—6.16 (m, 9 H, aromatic), 6.16 [s, 6-H(D)], 6.08 [t, 3-H(C), ΣJ_s 19.0 Hz], 5.06—4.62 [m, 3-H(F)], 4.87 [d, 2-H(F), *J* 8.5 Hz], 4.84 [d, 4-H(C), *J* 9.0 Hz], 4.80 [d, 2-H(C), *J* 10.0 Hz], 3.86, 3.82, 3.76, 3.73, 3.70, 3.62 (6 × s, 8 × OMe), 3.10 [dd, 4-eq-H(F), *J* 5.5 and 16.5 Hz], 2.58 [dd, 4-ax-H(F), *J* 9.0 and 16.5 Hz], 1.99(s) and 1.86(s) [Δν 10.0 Hz, 3-OAc(F)], and 1.66(s), 1.59(s) [Δν 5.0 Hz, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{285}$ 0, $[\theta]_{282}$ −303, $[\theta]_{280}$ 0, $[\theta]_{269}$ +3 939, $[\theta]_{249}$ 0, $[\theta]_{222}$ −50 909, and $[\theta]_{209}$ −10 606 (Found: C, 64.9; H, 6.2. Calculated for $C_{42}H_{46}O_{14}$ C, 65.1; H, 6.0%).

(−)-*Leucofisetinidin*–(+)-*Catechin Condensation*.—Coupling of (−)-leucofisetinidin (26) (580 mg) with (+)-catechin (3) (4.64 g) for 3 h afforded two bands, R_F 0.49 (242 mg, 22%) and 0.36 (322 mg, 28%). (*a*) The R_F 0.49 fraction consisted of a mixture of (2*S*,3*R*,4*S*)-2,3-*trans*-3,4-*cis*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (33) and (2*S*,3*R*,4*R*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-6-yl]flavan (30), which was methylated and subsequently resolved by p.l.c. [benzene–acetone (8 : 2)] into two fractions, R_F 0.31 (104 mg) and 0.19 (9 mg). The R_F 0.31 band consisted of the 4,8-linked 3,4-*cis*-heptamethyl ether (34) and the R_F 0.19 fraction of the 4,6-coupled all-*trans*-heptamethyl ether (31), both as colourless solids.

(2S,3R,4S)-2,3-trans-3,4-cis-3-*Acetoxy*-4-[(2S,3R)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3′,4′,7-*trimethoxyflavan* (35).—Acetylation of the 3,4-*cis*-heptamethyl ether (34) (90 mg) followed by p.l.c. separation [benzene–acetone (9 : 1)] afforded the *diacetate* (35), R_F 0.29, as a colourless solid (74 mg); *m/e* 744 (M^+, 33%), 684 (21), 624 (35), 522 (2.6), 491 (51), 462 (35), 449 (14.4), 431 (11.8), 387 (1.4), 357 (2.7), 327 (13.2), 300 (1.8), 297 (16.8), 269 (100), 222 (4.0), 180 (31), and 151 (87); δ (115 °C) 6.75—6.19 (m, 10 H, aromatic), 6.08 [s, 6-H(D)], 5.45 [dd, 3-H(C), *J* 7.0 and 8.5 Hz], 5.19—5.00 [m, 3-H(F)], 4.95 [d, 2-H(C), *J* 8.5 Hz], 4.94 [d, 4-H(C), $J_{3,4}$ 7.0 Hz], 4.68 [d, 2-H(F), *J* 7.8 Hz], 3.75, 3.74, 3.72, 3.70, 3.64 (5 × s, 7 × OMe), 3.04 [dd, 4-eq-H(F), *J* 5.8 and 16.3 Hz], 2.63 [dd, 4-ax-H(F), *J* 7.8 and 16.3 Hz], 1.83 [s, 3-OAc(F)], and 1.62 [s, 3-OAc(C)]; $\Delta G^{\ddagger}_{rot.}$ 18.04 kcal mol^{-1}; c.d. (MeOH) $[\theta]_{295}$ 0, $[\theta]_{289}$ 303, $[\theta]_{279}$ −1 666, $[\theta]_{263}$ −303, $[\theta]_{228}$ −47 272, and $[\theta]_{207}$ 0 (Found: C, 59.9; H, 6.3. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(2S,3R,4R)-2,3-trans-3,4-trans-3-*Acetoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,5,7-*tetramethoxyflavan*-8-*yl*]-3′,4′,7-*trimethoxyflavan* (32).—Acetylation of the all-*trans*-heptamethyl ether (31) (9 mg) gave the *diacetate* (36) (8 mg) as a colourless solid; *m/e* 744 (M^+, 3.4%), 684 (100), 624 (19.4), 491 (11.6), 462 (10.6), 449 (13.2), 431 (19.6), 387 (1.5), 357 (1.1), 327 (51), 300 (1.1), 297 (18), 269 (37), 222 (4.2), 180 (37), and 151 (99); δ (100 °C) 7.0—6.30 (m, 10 H, aromatic), 6.24 [s, 8-H(D)], 5.88 [t, 3-H(C), Σ J_s 19.6 Hz], 5.34—5.12 [m, 3-H(F)], 4.94 [d, 2-H(F), *J* 6.5 Hz], 4.80 [d, 4-H(C), *J* 9.8 Hz], 4.67 [d, 2-H(C), *J* 9.8 Hz], 3.80, 3.77, 3.76, 3.73, 3.66, 3.53 (6 × s, 7 × OMe), 2.95 [dd, 4-eq-H(F), *J* 5.5 and 16.0 Hz], 2.70 [dd, 4-ax-H(F), *J* 6.5 and 16.0 Hz], 1.81 [s, 3-OAc(F)], and 1.55 [d, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{295}$ 0, $[\theta]_{280}$ −5 454, $[\theta]_{251}$ 0, $[\theta]_{232}$ +46 969, and $[\theta]_{214}$ 0 (Found: C, 66.1; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(*b*) The R_F 0.36 fraction afforded the free phenolic (2S,3R,4R)-2,3-trans-3,4-trans-3,3′,4′,7-*tetrahydroxy*-4-[(2R,3S)-2,3-trans-3,3′,4′,5,7-*pentahydroxyflavan*-8-*yl*]-*flavan* (27) as a light brown solid. Methylation of the free phenol (260 mg) followed by p.l.c. [benzene–acetone (8 : 2)] gave the 4,8-linked all-*trans*-heptamethyl ether (28, R_F 0.19) as a white solid (93 mg). Acetylation of this methyl ether (90 mg) and p.l.c. separation [benzene–acetone (9 : 1)] afforded the *diacetate* (29), R_F 0.29, as a colourless amorphous solid (69 mg); *m/e* 744 (M^+, 2.5%), 684 (100), 624 (59), 491 (7.5), 462 (30), 449 (8.9), 431 (25), 327 (7.0), 300 (1.1), 297 (7.3), 269 (29), 180 (11.3), and 151 (36); δ (110 °C) 6.87—6.18 (m, 10 H, aromatic), 6.05 [s, 6-H(D)], 5.80 [t, 3-H(C), ΣJ_s 19.0 Hz], 5.30—5.05 [m, 3-H(F)], 4.79 [d, 4-H(C), *J* 9.5 Hz], 4.74 [d, 2-H(C), *J* 9.5 Hz], *ca.* 4.54 [2-H(F)], 3.77, 3.73, 3.66, 3.62 (4 × s, 7 × OMe), 2.95 [dd, 4-eq-H(F), *J* 5.5 and 16.3 Hz], 2.59 [dd, 4-ax-H(F), *J* 7.0 and 16.3 Hz], 1.81 [s, 3-OAc(F)], and 1.62 [s, 3-OAc(C)]; $\Delta G^{\ddagger}_{rot.}$ 17.01 kcal mol^{-1}; c.d. (MeOH) $[\theta]_{293}$ 0, $[\theta]_{282}$ +4 242, $[\theta]_{277}$ 0, $[\theta]_{267}$ −7 878, $[\theta]_{229}$ +45.454, and $[\theta]_{210}$ 0 (Found: C, 66.0; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(+)-*Mollisacacidin*–(−)-*Fisetinidol Condensation*.—Reaction of (+)-mollisacacidin (1) (400 mg) with (−)-fisetinidol (36) (1.88 g) for 2 h gave a single fraction, R_F 0.06 (364 mg, 46%), which consisted of the (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,7-tetrahydroxyflavan-6-yl]flavan (40) and the (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,7-tetrahydroxyflavan-6-yl]flavan (37).

Methylation of this free phenolic mixture (360 mg) followed by p.l.c. [benzene-acetone (8 : 2)] afforded three fractions, R_F 0.46 (22 mg), 0.30 (71 mg), and 0.25 (77 mg).

Acetylation of the R_F 0.46 fraction (20 mg) afforded the (2R,3S,4R)-2,3-trans-3,4-trans-3,3′,4′,7-*tetramethoxy*-4-[(2R,3S)-2,3-trans-3-*acetoxy*-3′,4′,7-*trimethoxyflavan*-8-*yl*]-

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flavan (38) as a colourless solid (19 mg); *m/e* 686 (M^+, 33%), 654 (5.2), 594 (1.7), 464 (1.9), 461 (100), 432 (8.0), 419 (37), 401 (16.1), 329 (1.2), 297 (11.2), 270 (1.2), 239 (10.1), 222 (3.6), 194 (99), 180 (38), and 179 (34); δ 7.09—6.28 (m, 11 H, aromatic), 5.41—5.09 [m, 3-H(F)], 4.94 [d, 2-H(F), *J* 7.0 Hz], 4.93 [d, 2-H(C), *J* 9.0 Hz], 4.80 [d, 4-H(C), *J* 9.0 Hz], 4.39 [t, 3-H(C), ΣJ_s 18.0 Hz], 3.87, 3.84, 3.75, 3.72, 3.19 (5 × s, 6 × OMe), 3.00 [dd, 4-eq-H(F), *J* 5.0 and 16.3 Hz], 2.73 [s, 3-OMe(C)], 2.72 [dd, 4-ax-H(F), *J* 7.5 and 16.3 Hz], and 1.89 [s, 3-OAc(F)].

Acetylation of the R_F 0.30 band (70 mg) and subsequent p.l.c. separation [benzene–acetone (9 : 1)] gave the 4,6-*linked* 3,4-cis-*hexamethyl ether diacetate* (41), R_F 0.44, as a colourless solid (25 mg); *m/e* 714 (M^+, 32%), 654 (56), 594 (8.1), 461 (100), 432 (7.4), 419 (34), 401 (17.3), 357 (2.1), 297 (22), 270 (2.3), 239 (8.9), 180 (97), and 151 (96); δ (360 MHz) 6.93—6.48 (9 H, aromatic), 6.57 [s, 5-H(D)], 6.49 [s, 8-H(D)], 5.54 [dd, 3-H(C), *J* 5.0 and 7.5 Hz], 5.33—5.27 [m, 3-H(F)], 5.15 [d, 2-H(C), *J* 7.5 Hz], 4.98 [d, 2-H(F), *J* 7.5 Hz], 4.81 [d, 4-H(C), *J* 5.0 Hz], 3.87, 3.86, 3.85, 3.84, 3.78, 3.72 (6 × s, 6 × OMe), 2.96 [dd, 4-eq-H(F), *J* 5.5 and 16.0 Hz], 2.76 [dd, 4-ax-H(F), *J* 8.0 and 16.0 Hz], 1.91 [s, 3-OAc (F)], and 1.78 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{300}$ 0, $[\theta]_{285}$ −4 242, $[\theta]_{276}$ 0, $[\theta]_{268}$ +3 939, $[\theta]_{255}$ +3 636, $[\theta]_{237}$ +63 939, and $[\theta]_{226}$ +3 939 (Found: C, 67.1; H, 6.1. $C_{40}H_{42}O_{12}$ requires C, 67.2; H, 5.9%).

Acetylation of the R_F 0.25 fraction (70 mg) afforded the 4,6-*coupled all*-trans-*hexamethyl ether diacetate* (39) (68 mg) as a colourless solid; *m/e* 714 (M^+, 2.0%), 654 (100), 594 (20), 461 (13.8), 432 (18.9), 419 (18.1), 401 (10.1), 297 (32), 270 (1.1), 239 (10.0), 222 (5.7), 180 (83), and 151 (84); δ (360 MHz) 7.02—6.46 (9 H, aromatic), 6.71 [s, 5-H(D)], 6.49 [s, 8-H(D)], 5.64 [t, 3-H(C), ΣJ_s 18.0 Hz], 5.34—5.25 [m, 3-H(F)], 5.0 [d, 2-H(C), *J* 9.0 Hz], 4.96 [d, 2-H(F), *J* 7.3 Hz], 4.57 [d, 4-H(C), *J* 9.0 Hz], 3.89, 3.88, 3.87, 3.86, 3.76, 3.75 (6 × s, 6 × OMe), 2.98 [dd, 4-eq-H(F), *J* 5.0 and 16.0 Hz], 2.74 [dd, 4-ax-H(F), *J* 8.0 and 16.0 Hz], 1.91 [s, 3-OAc(F)], and 1.68 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{303}$ 0, $[\theta]_{293}$ +2 121, $[\theta]_{288}$ 0, $[\theta]_{280}$ −3 636, $[\theta]_{272}$ 0, $[\theta]_{244}$ +15 151, $[\theta]_{237}$ 0, $[\theta]_{227}$ −33 939, and $[\theta]_{219}$ 0 (Found: C, 67.1; H, 6.0. $C_{40}H_{42}O_{12}$ requires C, 67.2; H, 5.9%).

(+)-*Mollisacacidin*–(+)-*Epifisetinidol Condensation*.—Coupling of (+)-mollisacacidin (1) (500 mg) with (+)-epifisetinidol (42) (940 mg) for 4.5 h gave a single fraction, R_F 0.28 (390 mg), which consisted of the (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-3,3′,4′,7-tetrahydroxy-4-[(2*S*,3*S*)-2,3-*cis*-3,3′,4′,7-tetrahydroxyflavan-6-yl]flavan (45) and (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*S*,3*S*)-2,3-*cis*-3,3′,4′,7-tetrahydroxyflavan-6-yl-]flavan (43). Methylation of this free phenolic mixture (350 mg) followed by p.l.c. separation [benzene–acetone (9 : 1)] also afforded a single fraction (116 mg) which was subsequently acetylated (100 mg) and the mixture resolved by p.l.c. [1,2-dichloroethane–acetone (97 : 3)] into two bands, R_F 0.22 (20 mg) and 0.18 (15 mg).

The R_F 0.22 fraction afforded the 4,6-*linked* 3,4-cis-*hexamethyl ether diacetate* (46) as a white solid; *m/e* 714 (M^+, 22%), 654 (43), 594 (6.8), 461 (64), 432 (5.1), 419 (22), 401 (9.4), 357 (2.0), 297 (18.8), 270 (1.4), 239 (7.9), 222 (6.6), 180 (65), and 151 (100); δ (360 MHz) 7.03—6.49 (9 H, aromatic), 6.61 [s, 5-H(D)], 6.54 [s, 8-H(D)], 5.55 [dd, 3-H(C), *J* 5.1 and 7.5 Hz], 5.42—5.39 [m, 3-H(F)], 5.17 [d, 2-H(C), *J* 7.5 Hz], 5.05 [s, 2-H(F)], 4.81 [d, 4-H(C), *J* 5.1 Hz], 3.91, 3.89, 3.87, 3.85, 3.80, 3.76 (6 × s, 6 × OMe), 3.17 [dd, 4-eq-H(F), *J* 4.5 and 17.5 Hz], 2.80 [dd, 4-ax-H(F), *J* 2.0 and 17.5 Hz], 1.94 [s, 2-OAc(F)], and 1.79 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{298}$ 0, $[\theta]_{287}$ −2 121, $[\theta]_{273}$ +1 010, $[\theta]_{255}$ 1 212, $[\theta]_{236}$ +42 424, $[\theta]_{210}$ 0 (Found: C, 67.0; H, 6.2. $C_{40}H_{42}O_{12}$ requires C, 67.2; H, 5.9%).

The R_F 0.18 fraction gave the 4,6-*coupled* 3,4-trans-*hexamethyl ether diacetate* (44) as a white solid; *m/e* 714 (M^+, 1.6%), 654 (100), 594 (11.7), 461 (10.1), 432 (11.7), 419 (11.9), 401 (6.2), 357 (1.2), 297 (20), 239 (4.4), 222 (3.3), 180 (56), and 151 (62); δ (360 MHz) 7.02—6.44 (9 H, aromatic), 6.61 [s, 5-H(D)], 6.51 [s, 8-H(D)], 5.71 [t, 3-H(C), ΣJ_s 18.0 Hz], 5.35 [m, 3-H(F), *J* <1 Hz], 5.04 [d, 2-H(C), *J* 8.5 Hz], 5.03 [s, 2-H(F)], 4.61 [d, 4-H(C), *J* 8.5 Hz], 3.89, 3.88, 3.87, 3.86, 3.77, 3.76 (6 × s, 6 × OMe), 3.12 [dd, 4-eq-H(F), *J* 4.5 and 17.3 Hz], 2.72 [dd, 4-ax-H(F), *J* 2.0 and 17.3 Hz], 1.89 [s, 3-OAc(F)], and 1.69 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{303}$ 0, $[\theta]_{292}$ +303, $[\theta]_{286}$ 0, $[\theta]_{277}$ −3 030, $[\theta]_{260}$ 0, $[\theta]_{247}$ +6 363, $[\theta]_{242}$ 0, $[\theta]_{230}$ −46 060, and $[\theta]_{200}$ −4 545 (Found: C, 67.1; H, 6.1. $C_{40}H_{42}O_{12}$ requires C, 67.2; H, 5.9%).

(+)-*Mollisacacidin*–(−)-*Epicatechin Condensation*.—Reaction of (+)-mollisacacidin (1) (580 mg) with (−)-epicatechin (47) (2.32 g) for 2 h afforded a single band, R_F 0.49 (610 mg) which consisted of the (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*R*)-2,3-*cis*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (48), (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*cis*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*R*)-2,3-*cis*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (53), and (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*trans*-3,3′,4′,7-tetrahydroxy-4-[(2*R*,3*R*)-2,3-*cis*-3,3′,4′,5,7-pentahydroxyflavan-6-yl]flavan (51). Methylation of this mixture (600 mg) followed by p.l.c. separation [benzene–acetone (8 : 2)] afforded three bands, R_F 0.55 (56 mg), 0.35 (204 mg), and 0.27 (206 mg).

Acetylation of the R_F 0.55 band (35 mg) followed by p.l.c. [benzene–acetone (9 : 1)] afforded the 4,6-*linked all*-trans-*octamethyl ether monoacetate* (52), R_F 0.42, as a white solid (2 mg); *m/e* 716 (M^+, 12%), 684 (17.3), 624 (6.4), 494 (1.9), 491 (100), 462 (16.3), 449 (29), 431 (16.4), 387 (1.5), 329 (4.8), 300 (1.5), 297 (12.2), 269 (74), 222 (2.9), 194 (98), 180 (23), and 179 (28); δ 7.02—6.30 (9 H, aromatic), 6.30 [s, 8-H(D)], 5.50—5.37 [m, 3-H(F)], 5.03 [s, 2-H(F)], 4.73 [d, 2-H(C), *J* 9.0 Hz], 4.52 [d, 4-H(C), *J* 9.0 Hz], 3.99 [t, 3-H(C), ΣJ_s 18.0 Hz], 3.89, 3.85, 3.78, 3.70, 3.48 (5 × s, 7 × OMe), 2.94 [s, 4-CH_2(F)], 2.66 [s, 3-OMe(C)], and 1.95(s), 1.81(s) [Δν 11.3 Hz, 3-OAc(F)].

This monoacetate (52) was accompanied by the related phenolic heptamethyl ether 3-methyl ether acetate (49), R_F 0.38 (20 mg) of the 4,8-linked all-*trans*-compound (48). Since the spectral characteristics are very similar to those of the closely related (7), they are not detailed.

The R_F 0.35 fraction (150 mg) was acetylated and the mixture resolved by p.l.c. [benzene–acetone (9 : 1)] to give the 4,8-*coupled* 3,4-trans-*heptamethyl ether diacetate* (50), R_F 0.33, as a white solid (93 mg); *m/e* 744 (M^+, 1.9%), 684 (85), 624 (56), 491 (8.2), 462 (35), 449 (13.2), 431 (31), 387 (2.8), 357 (1.5), 327 (19.2), 300 (3.3), 297 (15.9), 269 (53), 222 (4.1), 180 (33), and 151 (100); δ 7.08—6.23 (m, 9 H, aromatic), 6.12 [s, 6-H(D)], 6.12 [t, 3-H(C), ΣJ_s 20.0 Hz], 5.28—5.16 [s, 3-H(F)], 4.94 [s, 2-H(F), $J_{2,3}$ <1 Hz], 4.86 [2 × d, 2-H(C) and 4-H(C), *J* 10.0 Hz], 3.86, 3.82, 3.78, 3.74, 3.70, 3.68, 3.39 (7 × s, 7 × OMe), 3.02—2.73 [s, 4-CH_2(F)], 1.71 [s, 3-OAc(F)], and 1.55 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{232}$ −1 818, $[\theta]_{277}$ 0, $[\theta]_{267}$ +4 545, $[\theta]_{249}$ 0, $[\theta]_{232}$ −41 818, and $[\theta]_{215}$ −7 272 (Found: C, 66.1; H, 6.0. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

Acetylation of the R_F 0.27 fraction (150 mg) followed by

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p.l.c. separation [benzene–acetone (9 : 1)] afforded the 4,8-*coupled* 3,4-cis-*heptamethyl ether diacetate* (54), R_F 0.39, as a white solid (120 mg); *m/e* 744 (M^+, 26%), 684 (22), 624 (43), 522 (1.2), 491 (44), 462 (29), 449 (13.7), 431 (12.7), 387 (1.8), 357 (2.7), 327 (18.6), 300 (2.7), 297 (21), 269 (97), 222 (3.6), 180 (34), and 151 (100); δ 6.94—6.28 (m, 9 H, aromatic), 6.10 [s, 6-H(D)], 5.58 [dd, 3-H(C), *J* 5.0 and 6.8 Hz], 5.41 [d, 2-H(C), *J* 6.8 Hz], 5.30—5.20 [s, 3-H(F)], 4.77 [d, 4-H(C), *J* 5.0 Hz], 4.30 [s, 2-H(F)], 3.81, 3.80, 3.74, 3.72, 3.37 (5 × s, 7 × OMe), 2.97—2.78 [br s, 4-CH_2(F)], 1.86 [s, 3-OAc(F)], and 1.84 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{298}$ 0, $[\theta]_{279}$ −2 424, $[\theta]_{275}$ −303, $[\theta]_{258}$ −303, $[\theta]_{256}$ 0, $[\theta]_{238}$ +37 575, and $[\theta]_{224}$ 0 (Found: C, 66.0; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(−)-*Teracacidin*–(+)-*Catechin Condensation*.—Coupling of (−)-teracacidin (55, 500 mg) with (+)-catechin (3) (4.00 g) for 2 h affords two fractions, R_F 0.21 (87 mg, 9%) and 0.17 (398 mg, 41%). The former band gave the (2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*trans*-3,4′,7,8-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-6-yl]flavan (59) and the latter the (2*R*,3*R*,4*R*)-2,3-*cis*-3,4-*trans*-3,4′,7,8-tetrahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]-flavan (56), both as brown solids.

The 4,6-linked phenol (59) (80 mg) was methylated, the mixture resolved by p.l.c. [1,2-dichloroethane–acetone ×2 (17.5 : 2.5)] and the residual white solid (R_F 0.48, 39 mg) acetylated. P.l.c. separation [benzene–acetone (9 : 1)] gave the 4,6-*coupled* 3,4-trans-*heptamethyl ether diacetate* (60), R_F 0.40, as a white solid (26 mg); *m/e* 684 (M^+ −60, 100%), 624 (31), 522 (7.0), 521 (27), 479 (35), 462 (22), 461 (7.8), 357 (3.5), 330 (3.6), 327 (6.7), 297 (39), 299 (91), 222 (4.0), 192 (2.4), 180 (63), 150 (31), and 121 (98); δ 7.26—6.35 (m, 9 H, aromatic), 6.32 [s, 8-H(D)], 5.69—5.53 [m, 3-H(C)], 5.58 [s, 2-H(C)], 5.45—5.23 [m, 3-H(F)], 5.08 [d, 2-H(F), *J* 5.7 Hz], 4.50 [d, 4-H(C), *J* 4.5 Hz], 3.90, 3.84, 3.82, 3.79, 3,76, 3.59, 3.27 (7 × s, 7 × OMe), 2.82 [d, 4-CH_2(F), *J* 5.7 Hz], 1.98 [s, 3-OAc(F)], and 1.83 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{293}$ 0, $[\theta]_{281}$ −6 363, $[\theta]_{264}$ 0, $[\theta]_{233}$ +81 212, and $[\theta]_{214}$ 0 (Found: C, 66.0; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

Methylation of the 4,8-coupled free phenol (56) (390 mg) followed by p.l.c. separation [1,2-dichloroethane–acetone (17.5 : 2.5)] afforded two fractions, R_F 0.46 (15 mg) and 0.34 (178 mg). The R_F 0.46 band was acetylated and the residual white solids resolved by p.l.c. [1,2-dichloroethane–acetone (9 : 1)] to give the 4,8-linked octamethyl ether acetate (57), R_F 0.33, as a colourless solid (6 mg) with spectral (n.m.r. and m.s.) characteristics similar to those of the closely related (7).

Acetylation of the R_F 0.34 fraction and p.l.c. separation [1,2-dichloroethane–acetone (17.5 : 2.5)] afforded the 4,8-*coupled* 3,4-trans-*heptamethyl ether diacetate* (58), R_F 0.30, as an amorphous white solid (136 mg); *m/e* 744 (M^+, 5.3%), 684 (81), 624 (63), 522 (13.0), 521 (25), 479 (12.8), 462 (65), 461 (26), 357 (3.6), 330 (3.3), 299 (93), 297 (34), 222 (8.8), 192 (3.2), 180 (83), 151 (95), and 121 (100); δ 7.17—6.32 (m, 9 H, aromatic), 6.11 [s, 6-H(D)], 5.55 [dd, 3-H(C), *J* 2.5 and 4.0 Hz], 5.39 [d, 2-H(C), *J* 2.5 Hz], 5.28—5.11 [m, 3-H(F)], 4.65 [d, 2-H(F), *J* 7.0 Hz], 4.56 [d, 4-H(C), *J* 4.0 Hz], 3.79, 3,75, 3.73, 3.71, 3.69, 3.62 (6 × s, 7 × OMe), 3.09 [dd, 4-eq-H(F), *J* 5.5 and 16.5 Hz], 2.62 [dd, 4-ax-H(F), *J* 7.0 and 16.5 Hz], 1.87 [s, 3-OAc(F)], and 1.76 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{287}$ 0, $[\theta]_{269}$ −5 454, $[\theta]_{248}$ 0, $[\theta]_{230}$ +32 727, and $[\theta]_{221}$ 0 (Found: C, 66.0; H, 6.2. $C_{41}H_{44}O_{13}$ requires C, 66.1; H, 6.0%).

(+)-*Leucocyanidin*–(+)-*Catechin Condensation*.—(+)-Dihydroquercetin (1.013 g) (Senn Chemicals, Cat. No. 2226) was dissolved in ethanol (200 ml) and sodium borohydride (500 mg) added over a period of 30 min. After stirring for 1 h at room temperature, (+)-catechin (3) (3.865 g) and 0.1M HCl (400 ml) were added and stirring was continued for a further 30 min. Water (2 l) was added, the mixture extracted with ethyl acetate (4 × 200 ml), and dried (Na_2SO_4). P.l.c. separation afforded two bands, R_F 0.39 (96 mg) and 0.33 (292 mg).

The R_F 0.39 fraction consisted of (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-3,3′,4′,5,7-pentahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3′,4′,5,7-pentahydroxyflavan-6-yl]flavan (64) which was methylated and the mixture resolved by p.l.c. [benzene–acetone ×5 (8 : 2)]. Acetylation of the residual solid, R_F 0.47 (10 mg) followed by p.l.c. [benzene–acetone (9 : 1)] afforded the 4,6-*linked all*-trans-*octamethyl ether diacetate* (65), R_F 0.42, as a colourless solid (6 mg); *m/e* 774 (M^+, 1.3%), 714 (100), 654 (19.9), 521 (6.0), 492 (9.5), 479 (10.9), 461 (11.4), 330 (1.1), 327 (30), 299 (24), 222 (2.0), 180 (26), and 151 (86); δ 7.10—5.95 (m, 8 H, aromatic), 6.17 [s, 8-H(D)], 5.72 [dd, 3-H(C), *J* 9.3 and 10.0 Hz], 5.41—5.07 [m, 3-H(F)], 4.85 [d, 2-H(F), *J* 10.0 Hz], 4.72 [d, 4-H(C), *J* 9.3 Hz], 4.71 [d, 2-H(C), *J* 10.0 Hz], 3.85, 3.82, 3.70 (3 × s, 8 × OMe), 3.48—2.70 [m, 4-CH_2(F)], 1.72 [s, 3-OAc(F)], and 1.52 [s, 3-OAc(C)]; c.d. (MeOH) $[\theta]_{302}$ 0, $[\theta]_{285}$ −19 393, $[\theta]_{260}$ 0, $[\theta]_{241}$ −39 090, $[\theta]_{235}$ 0 (Found: C, 65.1; H, 6.1. $C_{42}H_{46}O_{14}$ requires C, 65.1; H, 6.0%).

The R_F 0.33 band consisted of the (2*R*,3*S*,4*R*)-2,3-*trans*-3,4-*trans*-3,3′,4′,5,7-pentahydroxy-4-[(2*R*,3*S*)-2,3-*trans*-3,3′,4′,5,7-pentahydroxyflavan-8-yl]flavan (62), which was methylated and the mixture resolved by p.l.c. [benzene–acetone (8 : 2)]. Acetylation of the residual solid, R_F 0.17 (90 mg) afforded the 4,8-coupled all-*trans*-octamethyl ether diacetate (63) as a colourless solid;[17] *m/e* 774 (M^+, 4.4%); δ 6.04 [s, 6-H(D)]; c.d. (MeOH) $[\theta]_{293}$ 0, $[\theta]_{281}$ −2 121, $[\theta]_{273}$ 0, $[\theta]_{270}$ 606, $[\theta]_{257}$ 606, $[\theta]_{254}$ 0, $[\theta]_{227}$ −46 667, and $[\theta]_{200}$ 7 272 (Found: C, 65.1; H, 6.0. Calculated for $C_{42}H_{46}O_{14}$: C, 65.1; H, 6.0%).

We thank the Council of Scientific and Industrial Research, Pretoria, for a research fellowship (J. J. B.), and the Wattle Bark Industry of South Africa Marketing Committee, Pietermaritzburg, and the Sentrale Navorsingsfonds of this University, for financial support.

[0/1059 *Received*, 7th *July*, 1980]

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